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Hypofractionated Three-Dimensional Conformal Radiation Therapy Alone for Centrally Located cT1-3N0 Non–Small-Cell Lung Cancer

Dongryul Oh, MD, Yong Chan Ahn, MD, PhD, BoKyong Kim, MD, PhD, and Hongryull Pyo, MD, PhD

Purpose: We retrospectively analyzed the treatment outcomes and toxicities by hypofractionated three-dimensional conformal radiation therapy (RT) alone in the patients with centrally located cT1-3N0 non–small-cell lung cancer (NSCLC).

Methods: Sixty patients with centrally located cT1-3N0 NSCLC received definitive RT alone at 3.0 Gy per fraction for either medical comorbidity or refusal of surgery, between January 2001 and December 2010. The central tumor was defined as being within 2 cm around the proximal bronchial tree. The median total dose was 60 (39–60) Gy.

Results: The local control (LC), overall survival (OS), and cause-specific survival rates at 2 and 5 years were 57.9%, 59.6%, 61.7%, and 50.1%, 33.5%, and 40.5%, respectively. Multivariate analyses showed that high cT stage ($p = 0.007$) and histology with NSCLC-not otherwise specified ($p = 0.008$) were the significantly unfavorable prognostic factors for OS, and that high cT stage ($p = 0.031$) and poor performance state ($p = 0.007$) were for LC. The LC rate at 2 years was 100% for cT1 tumor, 56.5% for cT2 tumor, and 28.6% for cT3 tumor, respectively. No patients experienced grade 3 or higher esophagitis, and three experienced grade 3 or higher pneumonitis.

Conclusion: Hypofractionated RT regimen for centrally located cT1-3N0 NSCLC proved safe with minimal toxicity, and, based on the excellent clinical outcomes in cT1 tumors, might serve as an alternative option for the patients who might not tolerate stereotactic body radiation therapy. As the clinical outcomes in cT2-3 tumors were still unsatisfactory, further dose intensifying regimen coupled with the use of concurrent systemic chemotherapy might be warranted.

Key Words: Non–small-cell lung cancer, Radiation therapy, Central tumors.

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Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

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Address for correspondence: Yong Chan Ahn, MD, PhD, Department of Radiation Oncology, Samsung Medical Center Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135–710, Korea. E-mail: ycahn.ahn@samsung.com; ahnyc@skku.edu

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Surgical resection has been the standard treatment for early-stage non–small-cell lung cancer (NSCLC). For patients who are medically inoperable because of medical comorbidity, or who decline surgery, however, definitive high-dose radiation therapy (RT) is the most appropriate curative alternative. The conventionally fractionated RT delivering 60 to 66 Gy for 6 to 7 weeks in daily doses of 1.8 or 2.0 Gy were commonly used. The conventionally fractionated RT, however, is known to achieve rather unsatisfactory clinical outcomes: 5% to 42% in 5-year overall survival (OS) rates; and 30% to 45% in local control (LC) rates.[1,2]

Stereotactic body radiation therapy (SBRT) is a specialized local ablative modality, in which highly focused and accurately controlled radiation beams are used to deliver a few fractions of very high fractional dose (10–20 Gy) and usually finishes within a week.[3] Recently, the application of SBRT to the patients with cT1-2N0 or selected cT3N0 NSCLC has become frequent, and has shown very promising clinical outcomes, with the LC rate of approximately 90% at a very low complication rate in many institutes.[4–8] The Radiation Therapy Oncology Group (RTOG) study, after SBRT with 54 Gy in three fractions, showed that the primary tumor control rate was 97.6% and the 3-year OS rate was 55.8%.[4] The patients with centrally located tumors or large-sized tumors, however, may not be the ideal candidates for SBRT because of the risk of excessive toxicities,[2,5,9] although several authors reported acceptable toxicity of SBRT for these tumors by dose modification with strict constraints for critical structures.[10,11]

Several institutions have reported favorable results in early-stage NSCLC by various hypofractionated regimens, which were different from the SBRT dose schedules, in the patients who might not tolerate SBRT.[12–16] These consist of more fractions by lower fractional doses (usually <10 Gy) than the SBRT dose schedules. At the author's institute, high-dose RT by daily 3.0 Gy has been used for the patients who are candidates of neither surgery nor SBRT, and our early experience of this regimen in early-stage NSCLC was previously reported.[17] In the current study, we analyzed the clinical outcomes by the abovementioned dosage schedule to the patients having centrally located tumors with no evident lymphatic metastasis.

PATIENTS AND METHODS

Patients

From January 2001 till December 2010, 275 NSCLC patients received high-dose definitive RT alone because of

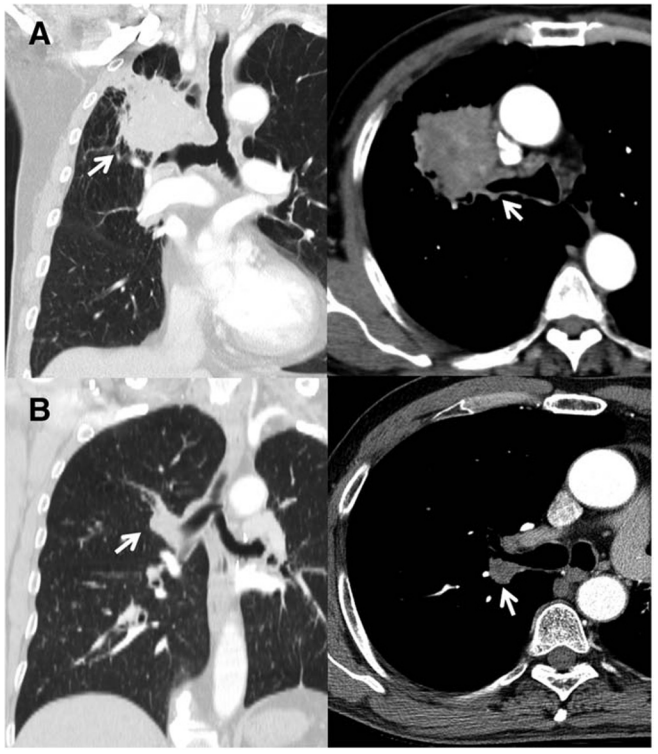

FIGURE 1. The axial and coronal computed tomography images in two patients with centrally-located tumors.

either medical comorbidity or refusal of surgery at the authors' institute. Among them, 60 patients had centrally located cT1-3N0 NSCLC and formed the basis of this retrospective study. The central tumor was defined as all or part of the gross tumor located within the proximal bronchial tree, which includes the lobar or greater bronchi plus 2 cm in all directions around. The typical cases were presented in Figure 1. Pathologic confirmation of NSCLC was made in all patients by bronchoscopy or percutaneous fine-needle aspiration and biopsy. The clinical stage was determined according to the 6th American Joint Committee on Cancer (AJCC) staging system. The diagnostic and staging workups included a complete history-taking and physical examination, simple chest radiographs, chest computed tomography (CT) scans (which covered the liver and adrenal glands), bronchoscopy, blood tests, bone scans, and brain magnetic resonance imaging.[18]Fluoro-deoxy-glucose positron emission tomography (PET) or PET/CT has been performed in almost every patient since 2003. As a result, 51 patients (85%) had PET or PET/CT.

Radiation Therapy

In all the patients, contrast-enhanced CT scans were performed in a supine position for simulation of three-dimensional conformal RT. CT images with 2.5 to 5.0 mm thickness were obtained during the quiet respiration. The clinical target volume (CTV) was delineated with a 3- to 5-mm margin in all directions around the gross tumor volume. Planning target volume was determined with adding a margin of 1.0 to 1.5 cm around the CTV to compensate for the respiratory movement and the set-up uncertainty. The addition of elective nodal irradiation (ENI) to the mediastinal lymphatics was individually determined per the physician's discretion, based on the clinical tumor size, location, and the histologic grade. The radiation dose was prescribed at the isocenter with the tissue heterogeneity corrections. The planned dosage was 60 Gy in once-daily 3.0 Gy doses during 4 consecutive weeks. Three or four beam arrangements were typically used to adequately cover the CTV while minimizing the dose to the normal tissues including the lung, the spinal cord, the heart, and the esophagus. The maximum dose to the spinal cord was not to exceed 45 Gy. For the lung, V_{20} (percentage of the total lung volume irradiated >20 Gy) ≤27.5% and the mean lung dose (MLD) of 16 Gy or lesser were preferred.[18] However, these lung constraints were not absolute requirements.

Follow-Up

The chest CT was performed for the evaluation of the initial response in 1 to 2 months of the RT completion, and the patients were followed up at 3 to 4 months' interval thereafter, with either chest CT or whole-body PET/CT. The treatment-related toxicities were graded according to the Common Terminology Criteria for Adverse Events, version 3.0.

Statistical Analysis

The survival rates were calculated by the Kaplan–Meier method. The duration of LC was from the first day of RT till the date of the first occurrence of local failure or the follow-up loss. The durations of OS and cancer-specific survival (CSS) were calculated from the first day of RT till the date of death by all causes or death by cancer progression or the treatment-related toxicities, respectively. The log-rank test was performed for univariate comparisons between the groups, and the Cox proportional hazards regression model was used for multivariate analysis. The distribution of categorical variables was analyzed by the χ^2 test. A p value of 0.05 or less was considered statistically significant. SPSS 19.0 (SPSS Inc., Chicago, IL) was used for the analysis.

RESULTS

Patient Characteristics

Among 60 patients who had centrally located cT1-3N0 NSCLC, the reasons for receiving RT alone were medical comorbidity in 56 patients (93.3%), and refusal of surgery in four (6.7%). The median follow-up period of all patients was 18 (1–96) months. Thirty-five patients (58.3%) were aged 70 years or older. Thirty-seven patients (61.7%) had Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1, whereas 23 (38.3%) had ECOG 2. Forty-four patients (73.3%) had squamous cell carcinoma. Forty-four patients (73.3%) received RT with the total dose of 60 Gy, and 14 (23.3%) received 54 Gy. Two patients (3.3%) received less than 54 Gy because of poor ECOG performance status. One patient stopped at 39 Gy and the other patient at 42 Gy. The ENI to the regional lymphatics was added to 19 patients (31.7 %), with the median dose of 30 (30–39) Gy. Dosimetric parameters of the lung could be obtained from 52 patients. In

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TABLE 1. Characteristics of All Patients

Characteristic	Number of Patients (%)
Age, yr	
<70	25 (41.7)
≥70	35 (58.3)
Gender	
Male	49 (81.7)
Female	11 (18.3)
Performance status	
0–1	37 (61.7)
2	23 (38.3)
T stage	
T1	10 (16.7)
T2	33 (55.0)
T3	17 (28.3)
Tumor size, cm	
≤3	22 (36.7)
> 3	38 (63.3)
Histology	
Squamous cell carcinoma	44 (73.3)
Adenocarcinoma	10 (16.7)
NSCLC-NOS	6 (10.0)
Total dose, Gy	
<54	2 (3.3)
54	14 (23.3)
60	44 (73.3)

NSCLC-NOS, non–small-cell lung cancer not otherwise specified.

these patients, the median V_{20} and MLD were 17.6% (6.7%–33.0%) and 997.5 cGy (454–1,570 cGy), respectively. The characteristics of all the patients are summarized in Table 1.

Toxicity

Grade 2 esophagitis occurred in 10 patients (16.7%), and none experienced esophagitis of grade 3 or more. Grade 2 pneumonitis developed in six patients (10.0%), grade 3 in two (3.3%), and grade 5 in one (1.7%). The patient who died of radiation pneumonitis was an 80-year-old woman, who was treated with a total dose of 54 Gy. She had 2.6-cm–sized tumor in the left upper bronchus, and the forced expiratory volume at 1 second and forced vital capacity were 1.44 liter/second and 2.51 liters. In 5 months after RT, she complained of cough and dyspnea, and the lung haziness within the RT volume and pleural effusion were shown on the CT scan. She was managed with steroid and her symptoms were wax and wane thereafter. In 12 months, her symptoms aggravated again and she eventually died of respiratory failure, without evidence of cancer progression. The dosimetric parameters of V_{20} and MLD were 33% and 15.5 Gy, respectively.

The addition of ENI resulted in increased toxicities of grade 2 or higher, although there was no significant statistical difference. For esophagtis, grade 2 toxicity developed in five of 19 patients (26.3%) in ENI (+) group, and in five of 41 patients (12.2%) in ENI (−) group (p = 0.126). For pneumonitis, grade 2 or higher toxicity developed in five of 19 patients (26.3%) in ENI (+) group and in four of 41 patients (9.8%) in ENI (−) group (p=0.263).

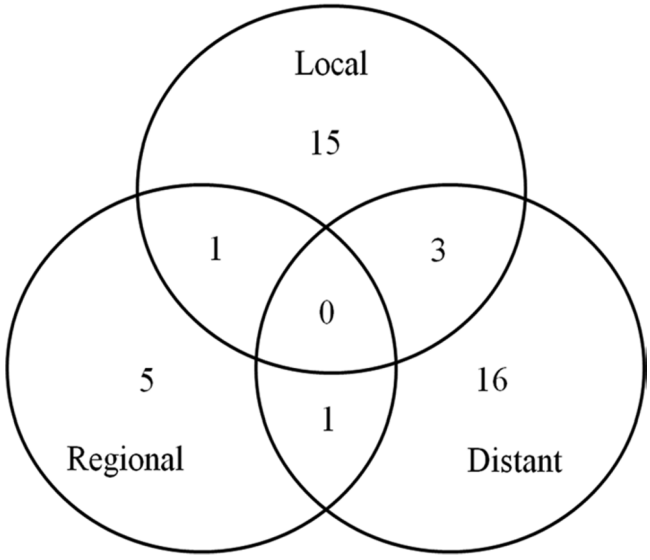

FIGURE 2. Pattern of failures at initial recurrence. OS, overall survival; CS, cancer-specific survival; LC, local control.

LC and Patterns of Failure

A total of 41 patients (68%) experienced failures. The initial relapses were local failure in 19 patients (31.7%), regional failure in seven patients (11.7%), and distant metastasis in 20 patients (33.3%), respectively (Fig. 2). Interestingly, the addition of ENI resulted in a decrease of regional recurrence as the first site of relapse. The regional failures occurred in one of 18 patients (5.2%) with ENI, and in six of 41 patients (14.6%) without ENI (p = 0.414). The sites of regional recurrence in these six patients were supraclavicular lymph node (n = 3), paraaortic lymph node (n = 1), paratracheal lymph node (n = 1), and hilar lymph node (n = 1).

The actuarial LC rates at 2 and 5 years were 57.9% and 50.1% (Fig. 3). Univariate analyses were performed on the patient age, sex, performance state, histology, total dose of radiation, cT stage, and the tumor size for the LC rate. The factors that showed a statistical significance on the 2-year LC rates included cT stage (100% for T1, 56.5% for T2, and 28.6% for T3; p = 0.003), tumor size (70.2% for tumor ≤3 cm and 46.9% for tumor >3 cm; p = 0.096), and performance status (72.9% for ECOG 0–1, 32.1% for ECOG 2; p = 0.002) (Fig. 4). Multivariate analysis showed that high cT stage (p = 0.031) and poor performance status (p = 0.007) adversely affected the LC significantly.

Survival

The median OS and CSS were 33 months and 33 months (Fig. 3). There were 25 cancer-specific deaths: disease progression in 21 patients; community-acquired pneumonia in three; and radiation pneumonitis in one. There were four deaths unrelated to lung cancer: chronic obstructive

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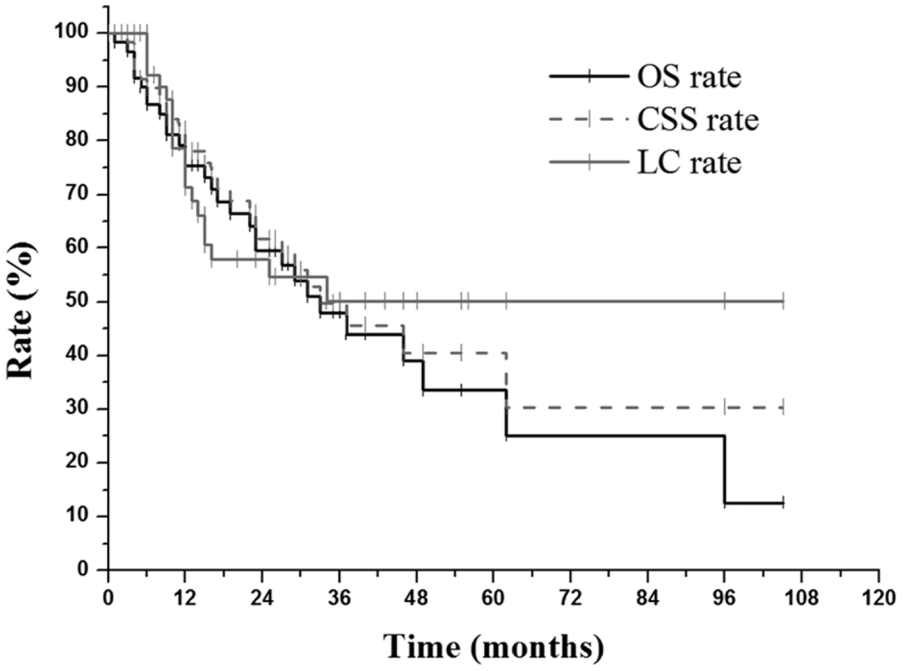

FIGURE 3. Overall survival, cancer-specific survival, and local control rate for all patients. ECOG, Eastern Cooperative Oncology Group.

pulmonary disease in one patient; hepatocellular carcinoma in one; pulmonary tuberculosis in one; and cerebral hemorrhage in one. The OS and CSS rates at 2 and 5 years were 59.6% and 61.7%, and 33.5% and 40.5%, respectively. Univariate analyses were performed on the patient age, sex, performance status, histology, total dose of radiation, the use of elective nodal irradiation, cT stage, and the tumor size for OS. The factors that showed a statistical significance on the 2-year OS rates included performance status (70.5% for ECOG 0–1, 40.3% for ECOG 2; $p = 0.041$), cT stage (87.5% for T1, 63.2% for T2, and 30.8% for T3; $p = 0.002$), tumor size (74.5% for tumor ≤3 cm and 49.7% for tumor >3 cm; $p = 0.011$), and histology (63.3% for squamous cell carcinoma, 60.0% for adenocarcinoma, and 33.3% for NSCLC-not otherwise specified [NOS]; $p = 0.011$). Multivariate analysis showed that high cT stage ($p = 0.007$) and histology with NSCLC-NOS ($p = 0.008$) were the significantly unfavorable prognostic factors for OS.

DISCUSSION

With the recent advances in the RT technique, SBRT, which has the advantages of high precision and accuracy, has been used more commonly in treating early-stage NSCLC.[4–8] The application of SBRT, however, is still challenging for the patients with centrally located or large-sized tumor, in fear of excessive toxicities.[2,9] In addition, there are some occasions when the patients poorly tolerate SBRT that needs tight immobilization for a longer treatment time per each fraction. For these patients, more protracted hypofractionated regimens with shorter treatment time can be the alternative, based on the favorable clinical results and the acceptable

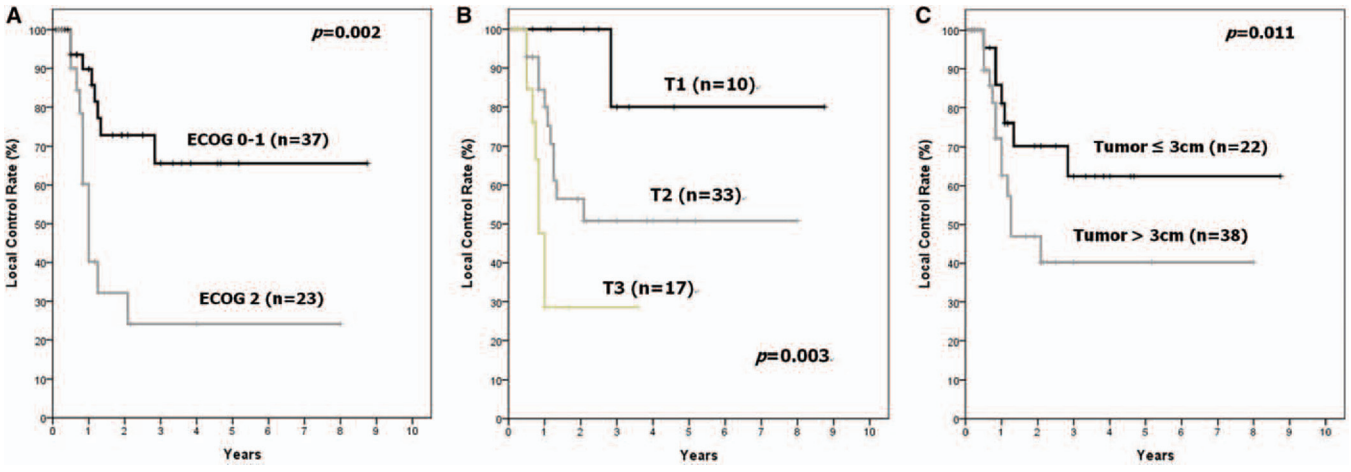

FIGURE 4. Local control rate according to (*A*), performance status, (*B*), cT stage, and (*C*) tumor size.

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TABLE 2. Recently Published Treatment Outcomes of Hypofractionated Radiation Therapy for Early-Stage Non–Small-Cell Lung Cancer

Study	Number of Patients (Lesions)	Stage	Location	RT Regimen (TD/DD)	Biologically Effective Dose ($\alpha/\beta = 10$)	Local Control
Bonfili et al.[11]	36	Stage I–II	Central, 10 peripheral, 26	60 Gy/3 Gy	78 Gy_{10}	63.9% at 2 yr
Soliman et al.[13]	118 (124)	T1–3N0	Central, 13 peripheral, 111	48–60 Gy/4 Gy	67.2–84 Gy_{10}	76.2% at 2 yr 70.1% at 5 yr
Milano et al.[12]	53 (98)	Stage I–III oligometastasis	Central, all	30–63 Gy/2.5–5 Gy (median 50 Gy/5 Gy)	Median 75 Gy_{10}	73.0% at 2 yr (all lesions)
Bogart et al.[10]	39	T1–2N0	Not mentioned	70 Gy/2.4– 4.11 Gy	86.9–98.8 Gy_{10}	92.3% (3 recurrences)
Present study	60	T1–3N0	Central, all	54–60 Gy/3 Gy	70.2–78 Gy_{10}	57.9% at 2 yr

DD, double drug; RT, radiation theraphy; TD, triple drug.

toxicity profiles.[12–17,19,20] At the author's institute, definitive RT alone at 3.0 Gy per fraction has been used for the patients with early-stage NSCLC, who are not candidates for either surgery or SBRT. Herein, we have shown the favorable survival outcomes: 5-year OS and CSS rates of 33.5% and 40.5%; and minimal toxicities. An excellent 2-year LC rate was achieved in cT1 tumors (100%), even though those for cT2 and cT3 tumors were not satisfactory (56.5% and 28.6%, respectively).

The treatment outcomes by more protracted hypofractionated RT schedules for early-stage NSCLC are summarized in Table 2. Soliman et al.[15] reported the long-term results of RT with 48 to 60 Gy, using a daily fraction of 4 Gy for stage I to II NSCLC. Only 11 of 124 tumors were centrally located. The 5-year CSS and LC rates were 59.8% and 70.1%, respectively. The 2-year LC rate was 82.5% for the tumors less than 3 cm and 66.9% for the tumors of 3 cm or more. Milano et al.[14] treated 53 patients with 98 central lung lesions including stage I to III NSCLCs and metastatic lung tumors. RT was delivered with the median total dose of 50 (30–63) Gy in 2.5 to 5 Gy per fraction. The 2-year LC rate of all lesions was 73%. Bonfili et al.[13] reported their results of RT with 60 Gy in 3 Gy per fraction for the elderly patients with stage I to II NSCLC. Ten of 36 patients had central tumors. The 2-year CSS and LC rates were 57.1% and 63.9%, respectively. Cancer and Leukemia Group B (CALGB) 39904[12] prospectively evaluated the accelerated regimen for the patients with stage I NSCLC (<4 cm with pulmonary dysfunction). The dose per fraction was escalated from 2.41 Gy to 4.11 Gy with the total dose of 70 Gy. Local failure occurred in three of 39 patients (7.7%).

Overall, the LC rate of approximately 60% to 70% was achieved when more protracted hypofractionated treatment regimens were used for early-stage NSCLCs (Table 2). The LC rate is thought to be lower when compared with SBRT, which may be because of insufficient total RT dose. Biologically effective doses (Gy_{10}, $\alpha/\beta = 10$) in most hypofractionated regimens ranged from 70 to 85 Gy_{10}, although biologically effective doses larger than 100 Gy_{10} are needed for improved LC.[21,22] For the small tumors, however, hypofractionated regimen also showed the excellent outcomes of the LC rate higher than 80%. In the current study, the 2-year LC rate was 100% for cT1 tumor, 56.5% for cT2 tumor, and 28.6% for cT3 tumor, respectively. Despite limitations in small numbers of patients with cT1 tumors ($n = 10$), it is noted that there was only one local failure, which occurred in 34 months after a dosage of 54 Gy/18 fractions

The patients with centrally located tumors are not good candidates for SBRT, because of previously reported high risk of severe toxicities. Timmerman et al.[2] reported that when SBRT was delivered with 60 to 66 Gy in three fractions, 14 patients experienced grade 3 to 5 toxicities which included pneumonia, pleural effusion, apnea, skin reaction, pericardial effusion, massive hemoptysis, and decline in pulmonary function test. The authors showed that the probability of grade 3 to 5 toxicities at 2 years was 46% for the central tumors and 17% for the peripheral tumors; however, they did not describe the difference in the toxicity profiles between the central and peripheral tumors and the reasons why the patients with central tumors experienced more toxicities. Naturally, the major airway is one of the most problematic organs at risk when SBRT has to be applied to the centrally located tumors. Mcgarry et al.[23] reported one case of symptomatic bronchitis after SBRT of 60 Gy in three fractions and one case of tracheal necrosis after SBRT of 72 Gy in three fractions in a phase I dose-escalation study. Song et al.[9] reported that complete or partial bronchial stricture developed in eight of nine patients (88.9%) who had central tumors, when treated with 40 to 60 Gy in three to four fractions. They also reported that one patient experienced death because of bleeding and two patients experienced grade 3 to 4 toxicity of bronchial stricture and secondary obstructive pneumonia. These major airway toxicities were sporadically reported even in the patients treated with conventional[24,25] or hyperfractionated RT,[26] and more often in the patients receiving endobronchial brachytherapy.[27,28] The total irradiated dose to airway, which was higher than 80 Gy[26] and dose per fraction[27] might have been the significant risk factors for the airway toxicity. On the basis of the data published to date, it seems that more protracted hypofractionated regimens are associated with more acceptable toxicity profiles for the centrally located tumors. Milano et al.[14] reported that fatal pulmonary toxicity occurred in four of 57 patients with central tumors, when treated with the median dose of 50 (30–63) Gy in 2.5 Gy to 5.0 Gy per fraction. Two patients died from grade 5 dyspnea, one from bronchitis and one from fatal hemoptysis. According to the authors, all the patients who experienced fatal toxicity received multiple courses of RT. Bonfili et al.[13] reported that no grade 3 or higher toxicity occurred when using 60 Gy in

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3.0 Gy per fraction in 10 patients with the central tumors. Our data also showed acceptable toxicity. Grade 3 or higher toxicity developed in three patients (5.0%), one of whom died of radiation pneumonitis. Consequently, in the patients with the centrally located tumors, more protracted hypofractionated regimen ranging from 70 to 85 Gy_{10} may have reduced the incidence of severe toxicity including the major airway toxicity. Instead, the LC rate was lower than SBRT. A further dose escalation at no increased risk of severe toxicity will be needed to determine the therapeutic window. In our institute, a dose per fraction has recently been increased from 3.0 to 4.0 Gy with a total dose up to 60 Gy.

Recently, risk-adaptive SBRT was applied to the centrally located tumors.[10] It showed that a 2-year LC rate of 85% and no grade 4 or 5 toxicity after SBRT to 63 patients with the central lung lesions, when the maximum dose in 0.5 cm^3 of the organs at risk was restricted to 6 to 7 Gy per fraction for the esophagus, 8 to 10 Gy for the trachea, and 8 to 12 Gy for the main bronchi. "Risk-adaptive" regimen indicates the SBRT dose modification with strict dose constraints for the critical structures. This approach should ideally be addressed in a prospective study to determine the optimal dose schedule in treating the central lung tumors. The ongoing trial of SBRT for centrally located tumors (RTOG 0813) is expected to give us further evidence on this issue.

In conclusion, hypofractionated RT using 3.0 Gy per fraction to centrally located cT1-3N0 NSCLC proved safe with minimal toxicity, and, based on the excellent clinical outcomes in cT1 tumors, might serve as an alternative option for patients who might not tolerate SBRT. The clinical outcomes in cT2–3 tumors, however, were still unsatisfactory, and further dose-intensifying regimen coupled with the use of concurrent systemic chemotherapy might be warranted.

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